

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



**Europäisches
Patentamt**

**European
Patent Office**

**Office européen
des brevets**

111522

Bescheinigung

Certificate

Attestation

Die angehefteten Unterla-
gen stimmen mit der
ursprünglich eingereichten
Fassung der auf dem näch-
sten Blatt bezeichneten
europäischen Patentanmel-
dung überein.

The attached documents
are exact copies of the
European patent application
described on the following
page, as originally filed.

Les documents fixés à
cette attestation sont
conformes à la version
initialement déposée de
la demande de brevet
européen spécifiée à la
page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03016226.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

THIS PAGE BLANK (USPTO)



Anmeldung Nr:
Application no.: 03016226.7
Demande no:

Anmeldetag:
Date of filing: 17.07.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Pharmaceutical composition of antiviral agents

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

Boehringer Ingelheim Case 1-1522 Prio

- 1 -

PHARMACEUTICAL COMPOSITION OF ANTIVIRAL AGENTS

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition
5 useful for the treatment of viral infections comprising
nevirapine and at least one antiviral active compound of
formula (I). Furthermore the present invention relates to a
use of nevirapine in combination or alternation with a
compound of formula (I) in the prophylaxis or treatment of a
10 viral infection in a patient. The present invention also
relates to a use of nevirapine in combination with a compound
of formula (I) for the manufacture of a medicament for the
prophylaxis or treatment of a viral infection in a patient. In
addition the present invention relates to a kit of parts and
15 to a manufacture for the prophylaxis or treatment of a viral
infection in a patient.

BACKGROUND OF THE INVENTION

20 Human immunodeficiency virus (HIV) is recognized as the
causative agent in AIDS.

Current therapies for HIV infection focus on inhibiting the
activity of viral enzymes which are essential to the life
25 cycle of the virus. The agents that are presently in use fall
mainly into three classes, designated Nucleoside Reverse
Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse
Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors
(PIs). Presently, combination therapies, i.e. the selection of
30 two or more antiretroviral agents taken together to make up a
"drug cocktail," are the preferred treatment for HIV
infection. Combination therapies have been shown to reduce the
incidence of opportunistic infections and to increase survival
time. Typically, the drug cocktail combines drugs from
35 different classes, so as to attack the virus at several stages
in the replication process. This approach has been shown to

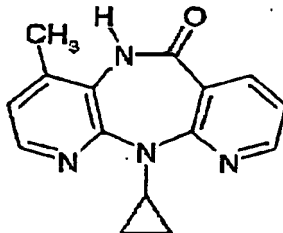
Boehringer Ingelheim Case 1-1522 Prio

- 2 -

reduce the likelihood of the development of virus forms that are resistant to a given drug or class of drugs.

Treatment failure with rebound of the amount of HIV which can
5 be measured in the blood is common for patients treated with
combination antiretroviral regimens. Resistance to the drugs
in the drug regimen develops as the virus replicates in the
presence of these drugs. Because of structural similarities of
the drugs within an antiretroviral class, cross resistance is
10 commonly seen to the other members of that class (for example
virologic failure on a regimen containing an NNRTI will lead
to cross resistance to the other first generation NNRTI
agents). As patients experience repeated virologic failure on
antiretroviral combination therapy, their viruses develop
15 broad multi-class antiretroviral drug resistance which limits
the effectiveness of the next round of antiretroviral therapy.
Many highly treatment experienced patients have been exposed
to all three classes of antiretroviral drugs and cannot obtain
two active drugs to form the core of a new, effective
20 antiretroviral drug regimen.

Nevirapine (Viramune®) is a non-nucleoside inhibitor of HIV
reverse transcriptase, which is useful in the treatment of HIV
infection in humans. The chemical name for nevirapine is
25 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-
e][1,4]diazepin-6-one. Its structural formula is:

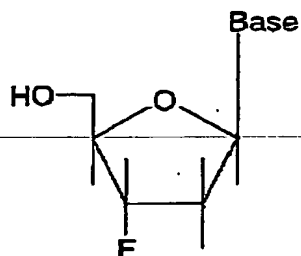


30 The earliest known synthesis of nevirapine, by Hargrave et
al., is described in US Patent 5,366,972.

Boehringer Ingelheim Case 1-1522 Prio

- 3 -

Furthermore compounds of the formula (I)



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, are described in the WO 88/00050 and WO 91/01137 for the therapeutic and prophylactic control and treatment of AIDS, HIV infections, hepatitis B virus (HBV) infections and retrovirus infections in animals and man. These nucleoside compounds are transformed by cells or enzymes to triphosphates which inhibit the reverse transcriptase of retrovirus as well as the activity of DNA dependent polymerase of hepatitis B virus.

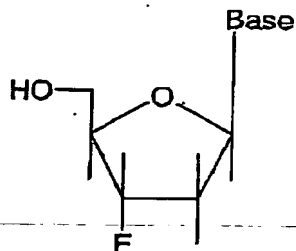
Combinations of nevirapine with at least one compound of the formula (I) which exhibit potent therapeutic activity against HIV and HBV would greatly aid in the development of new combination therapy against human retroviral (HRV) infections and HBV.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a novel pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)

Boehringer Ingelheim Case 1-1522 Prio

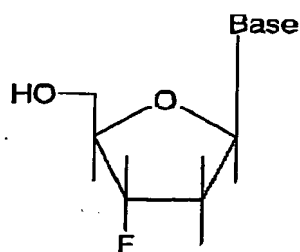
- 4 -



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or
5 prodrug thereof.

The pharmaceutical compositions of the present invention are useful in therapy, in particular as antivirals, especially in the treatment or prophylaxis of human retroviral (HRV)
10 infections.

In a second aspect, there is provided a use of nevirapine in combination or alternation with at least one antiviral active compound of formula (I)
15



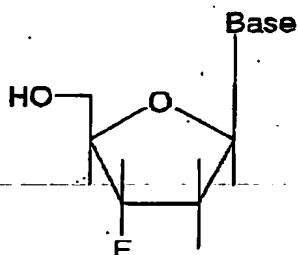
I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or
20 prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

In a third aspect, there is provided a use of nevirapine in combination with at least one antiviral active compound of
25 formula (I)

Boehringer Ingelheim Case 1-1522 Prio

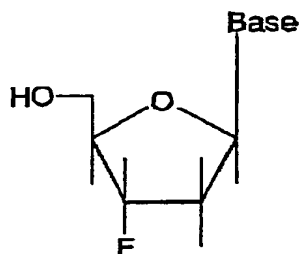
- 5 -



I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

- In a fourth aspect of this invention, there is provided a kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising
- (a) a first containment containing a pharmaceutical composition comprising nevirapine and at least one pharmaceutically acceptable carrier, and
 - (b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)



I

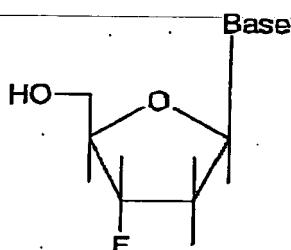
- wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier.

Boehringer Ingelheim Case 1-1522 Prio

- 6 -

In a fifth aspect of this invention, there is provided a manufacture comprising nevirapine and at least one antiviral active compound of formula (I)

5



I

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

With the combination of nevirapine and a compound of the formula (I) according to this invention, including its use in prophylaxis and treatment, the person skilled in the art can achieve an advantageous therapeutic effect to inhibit viral replication, especially of human retrovirus (HRV) and HBV, in particular of multiresistant HIV. In most cases, the enhanced therapeutic effect is not attainable by administration of either agent alone. In a preferred but not necessary embodiment, the effect of administration of nevirapine and the compound of formula (I) in combination or alternation is synergistic. Even though a combination exhibits additive and not synergistic effects, the combination can still provide an effect that is different from the separate administration of the two agents. For example, the biodistribution, pharmacokinetics, cytotoxic effects or metabolism of one can be affected by the other.

Boehringer Ingelheim Case 1-1522 Prio

- 7 -

Further aspects of the present invention become apparent to the one skilled in the art from the following detailed description and examples.

5 DEFINITIONS

The term "pharmaceutically acceptable salt" means a salt of the corresponding compound which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts.

15 Lists of suitable salts are found in, e.g., S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

As used herein, the term "treatment" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention to alleviate or eliminate symptoms of the viral infection and/or to reduce viral load in a patient.

25 As used herein, the term "prevention" or "prophylaxis" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood.

As used herein, the term "human retrovirus" (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell

35

Boehringer Ingelheim Case 1-1522 Prio

- 2 -

leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

5

DETAILED DESCRIPTION OF THE INVENTION

The virally active agents according to this invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the art. Furthermore, the virally active agents according to this invention may also be used as in form of their pharmacologically acceptable salts and/or hydrates.

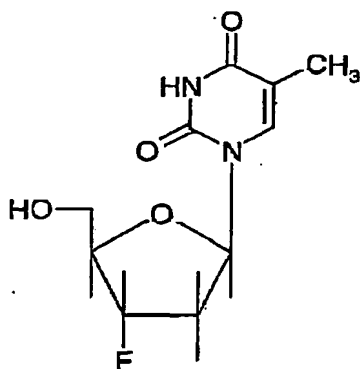
10

15

According to the first aspect of this invention, there is provided a novel pharmaceutical composition useful for the treatment of viral infections comprising nevirapine and at least one antiviral active compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

20

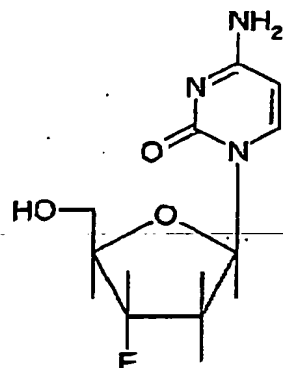
The following known compounds constitute part of the invention as preferred compounds of the formula (I) to be combined with nevirapine:



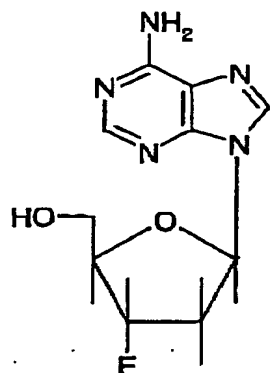
3'-deoxy-3'-fluorothymidine (FLT)

Boehringer Ingelheim Case 1-1522 Prio

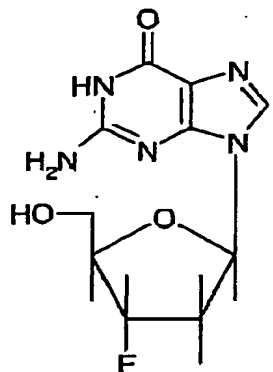
- 9 -



2',3'-dideoxy-3'-fluorocytidine



2',3'-dideoxy-3'fluoroadenosine

2',3'-dideoxy-3'-fluoroguanosine
(FLG)

including pharmaceutically acceptable salts and prodrugs of the compounds listed above.

- 5 Preferred prodrugs of FLG are described in WO 99/09031 and WO 99/41268, which documents in their entirety are incorporated herein by reference.

Boehringer Ingelheim Case 1-1522 Prio

- 10 -

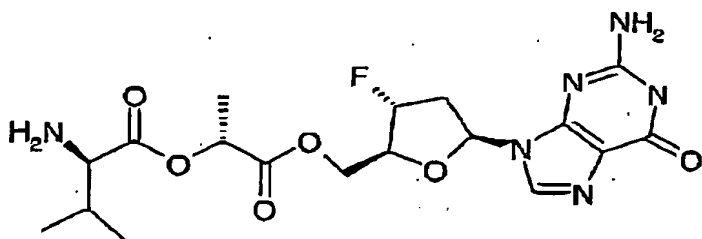
The most preferred compound of the formula (I) to be combined with nevirapine according to the aspects of this invention is selected from the group consisting of

(a) 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and

(b) 2',3'-dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

The compound of the formula (I) is very most preferably selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, including pharmaceutically acceptable salts thereof.

3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine is a preferred prodrug of FLG and can be depicted by the following structure



The synthesis of 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, also named as 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, is described in the WO 99/09031 and especially in example 32 therein.

Therefore, a preferred pharmaceutical composition useful for the treatment of viral infections comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-

Boehringer Ingelheim Case 1-1522 Prio

- 11 -

valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof.

Furthermore, nevirapine in combination or alternation with preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, is used in the prophylaxis or treatment of a viral infection in a patient.

- Also preferred is the use of nevirapine in combination with 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

- A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises
- (a) a first containment containing a pharmaceutical composition comprising nevirapine and a pharmaceutically acceptable carrier, and
 - (b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

- A preferred manufacture comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in a patient.

- The advantageous effects of the combination of nevirapine and the compound of formula (I) are realized over a wide ratio, like for example in a ratio of between 1:250 to 250:1.

Boehringer Ingelheim Case 1-1522 Prio

- 12 -

Therefore, in the compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention, nevirapine and the at least one compound of formula (I), which is preferably 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, are preferably present in a synergistic ratio. Usually, this ratio is between about 1:250 to about 250:1. More preferably the ratio is between about 1:50 to about 50:1. The most preferred ratio is between about 1:20 to about 20:1, which includes the ratios 1:18, 1:16, 1:14, 1:12, 1:10, 1:8, 1:6, 1:5, 1:4, 1:3, 1:2,5; 1:2, 1:1,5; 1:1,2; 1:1; 1,2:1; 1,5:1; 2:1; 2,5:1; 3:1; 4:1; 5:1; 6:1; 8:1; 10:1, 12:1, 14:1, 16:1, 18:1 and all ranges in between. If a further therapeutic agent is added, ratios will be adjusted accordingly.

It will be appreciated that the amount of pharmaceutical composition according to the invention required for use in treatment or prophylaxis will vary not only with the particular compound selected but also with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician or veterinarian. In general however the active compounds are included in the pharmaceutically acceptable carrier in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication in vivo, especially HIV replication, without causing serious toxic effects in the treated patient. By "inhibitory amount" is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein. A suitable dose will preferably be in the range of from about 0.05 to about 200 mg/kg of body weight per day.

The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate

Boehringer Ingelheim Case 1-1522 Prio

- 13 -

intervals, for example as two, three, four or more doses per day.

5 The pharmaceutical composition according to the present invention is conveniently administered in unit dosage form; for example containing 5 to 3000 mg, conveniently 5 to 1000 mg of active ingredient(s) per unit dosage form.

10 The pharmaceutical acceptable carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Examples of pharmaceutically acceptable carriers are magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Carriers which are suited to achieve a sustained release, for
15 example natural or synthetic polymers or liposomes, are known to the one skilled in the art. Pharmaceutically acceptable carriers also comprise liquid carriers and diluents, for example water, alcohol, glycerine or oil, which serve as a base for liquid formulations, such as solutions, suspensions
20 or emulsions.

The compositions referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and therefore pharmaceutical formulations
25 comprising a composition as defined above together with a pharmaceutically acceptable carrier comprise a further aspect of the invention.

The individual components of such compositions may be
30 administered either in combination, i.e. simultaneously, or in alternation, i.e. sequentially, in separate or combined pharmaceutical formulations.

When nevirapine is used in combination with a compound of the
35 formula (I) against the same virus the dose of each compound may be either the same as or differ from that when the

Boehringer Ingelheim Case 1-1522 Prio

- 14 -

compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compositions according to this invention preferably also
5 comprise at least one pharmaceutically acceptable carrier.

According to the third aspect of this invention, the combination of nevirapine and at least one compound of the formula (I) is used for the manufacture of a medicament for
10 the prophylaxis or the treatment of a viral infection in a patient.

According to one embodiment, this medicament may be a unit dosage form, which is preferably useful in combination
15 therapy, such as capsules or tablets. The unit dosage form contains a pharmaceutical composition according to this invention, i.e. nevirapine in combination with at least one compound of the formula (I), with at least one pharmaceutically acceptable carrier.

20 Therefore, another object of this invention also comprises bringing nevirapine and at least a compound of the formula (I) together in conjunction or association with a pharmaceutically acceptable carrier.

25 According to another embodiment, this medicament is a multiple dosage form, preferably a kit of parts, which is especially useful in alternation and/or combination therapy to flexibly suit the individual therapeutic needs of the patient.

30

Boehringer Ingelheim Case 1-1522 Prio

- 15 -

According to one embodiment the combinations, compositions,
kit of parts, manufactures of this invention and the uses
thereof, which comprise nevirapine and at least one compound
of the formula (I), or a pharmaceutically salt or prodrug
5 thereof, further comprise a further nucleoside reverse
transcriptase inhibitor (NRTI), preferably other than 3'-
deoxy-3'-fluorothymidine.

10 Following this, a preferred pharmaceutical composition useful
for the treatment of viral infections comprises nevirapine in
combination with 3'-deoxy-3'-fluorothymidine and a further
NRTI, or a pharmaceutically acceptable salt or prodrug
thereof.

15 Furthermore, nevirapine in combination or alternation with
preferably 3'-deoxy-3'-fluorothymidine and a further NRTI, or
a pharmaceutically acceptable salt or prodrug thereof, is used
in the prophylaxis or treatment of a viral infection in a
patient.

20 Also preferred is the use of nevirapine in combination with
3'-deoxy-3'-fluorothymidine and a further NRTI, or a
pharmaceutically acceptable salt or prodrug thereof, for the
manufacture of a medicament for the prophylaxis or treatment
25 of a viral infection in a patient.

A preferred kit of parts for the prophylaxis or treatment of a
viral infection in a patient, comprises
(a) a first containment containing a pharmaceutical
30 composition comprising nevirapine and a pharmaceutically
acceptable carrier; and
(b) a second containment containing a pharmaceutical
composition comprising 3'-deoxy-3'-fluorothymidine and a
further NRTI, or a pharmaceutically acceptable salt or prodrug
35 thereof, and a pharmaceutically acceptable carrier.

Boehringer Ingelheim Case 1-1522 Prio

- 16 -

Another preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises

- (a) a first containment containing a pharmaceutical composition comprising nevirapine and a pharmaceutically acceptable carrier; and
 - (b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier; and
 - (c) a third containment containing a pharmaceutical composition comprising a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.
- A preferred manufacture comprises nevirapine, 3'-deoxy-3'-fluorothymidine and a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

- In the foregoing and in the following, the term "a further NRTI" refers to a nucleoside reverse transcriptase inhibitor, or a pharmaceutically acceptable salt or prodrug thereof, other than 3'-deoxy-3'-fluorothymidine. Examples of further NRTIs are AZT, ddI, d4T, ddC, 3TC, FLG, Abacavir, including Abacavir sulfate, Tenofovir, including Tenofovir disoproxil and/or Tenofovir disoproxil fumarate, Emtricitabine, Amdoxovir/DAPD, Ach-126443 and including those NRTIs listed hereinafter. Preferred further NRTI are selected from the group consisting of AZT, ddI, 3TC, ddC, d4T and FLG, including its pharmaceutically acceptable salts and prodrugs.

- In case the selected compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, then the preferred "further NRTI" is 2',3'-dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-

Boehringer Ingelheim Case 1-1522 Prio

- 17 -

fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

In case the selected compound of the formula (I) is 2',3'-
5 dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof, then the preferred "further NRTI" is 3'-deoxy-3'-fluorothymidine, or a
10 pharmaceutically acceptable salt or prodrug thereof.

In a still further embodiment, the pharmaceutical compositions of the present invention may comprise at least one further antiviral agent. The further antiviral agent is preferably
15 chosen from the group consisting of NRTIs (nucleoside-analogue reverse transcriptase inhibitors), NNRTIs (non nucleoside reverse transcriptase inhibitors) and protease inhibitors.

Examples of further antiviral agents are 3TC (lamivudine), AZT
20 (zidovudine), FTC (5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine), d4T (2',3'-dideoxy-2',3'-didehydrothymidine, stavudine and Zerit), nevirapine, DMP-226, nelfinavir, delavirdine, including delavirdine mesylate, 9-[(2-hydroxymethyl)-1,3-dioxolan-4-yl]guanine, 2-amino-9-[(2-
25 hydroxymethyl)-1,3-dioxolan-4-yl]adenine, MKC-442, 1592U89 (abacavir), 141W94, MK-639, EMS-234475, PNU-140690, ABT-378, DMP-450, lopinavir, Indinavir, saquinavir, including saquinavir mesylate, ritonavir, efavirenz (sustiva), TIBO, HEPT, BHAP, a-APA, TSAO, calanolides, L-697,661, 2',3'-
30 dideoxycytidine (ddC or zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI or didanosine), 3'-deoxythymidine, 2',3'-dideoxy-2',3'-didehydrocytidine, ribavirin, DMP-450 (Triangle Pharmaceuticals, Inc.), 141W94 (amprenavir, GlaxoWellcome, Inc.), Rescriptor (delavirdine), abacavir
35 (1592U89), carbovir, CS-92 (3'-azido-2',3'-dideoxy-5-methylcytidine), b-D-dioxolane nucleosides such as b-D-dioxolanylguanine (DXG), b-D-dioxolanyl-2,6-diaminopurine

Boehringer Ingelheim Case 1-1522 Prio

- 18 -

(DAPD), and b-D-dioxolanyl chloropurine (ACP); acyclic nucleosides such as acyclovir, ganciclovir; interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as probenecid; nucleoside transport inhibitors
5 such as dipyridamole; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine, 1-deoxynojirimycin; and inhibitors of HIV
10 binding to CD4 receptors such as soluble CD4, CD4 fragments, CD4-hybrid molecules and inhibitors of the HIV aspartyl protease such as L-735,524.

The further antiviral agent is preferably chosen from
15 zidovudine, didanosine, zalcitabine, stavudine, lamivudine, lopinavir, delavirdine, including delavirdine mesylate, nevirapine, delavirdine, efavirenz, indinavir, nelfinavir, including nelfinavir mesylate, amprenavir and saquinavir, including saquinavir mesylate.

20 The compounds, or their pharmaceutically acceptable derivative or salts thereof, can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as
25 antibiotics, antifungals, antiinflammatories, protease inhibitors, or other nucleoside or non-nucleoside antiviral agents, as discussed in more detail above.

In general, during alternation therapy, an effective dosage of
30 each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on such factors as absorption, biodistribution, metabolism and excretion rates for each drug as well as other factors known to those of skill
35 in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject,

Boehringer Ingelheim Case 1-1522 Prio

- 19 -

specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Examples of suitable
5 dosage ranges for nevirapine, compounds of formula (I), preferably 3'-deoxy-3'-fluorothymidine, further NRTIs and other antivirals can be found in the scientific literature. Many examples of suitable dosage ranges for other compounds described herein are also found in the public literature or
10 can be identified using known procedures. These dosage ranges can be modified as desired to achieve a desired result.

It has been recognized that drug-resistant variants of HIV can emerge after prolonged treatment with an antiviral agent. Drug
15 resistance most typically occurs by mutation of a gene that encodes for an enzyme used in the viral life cycle, and most typically in the case of HIV, in either the reverse transcriptase or protease genes. It has been demonstrated that the efficacy of a drug against HIV infection can be prolonged,
20 augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation(s) from that selected for by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the
25 drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. In the case of administering the antiviral compounds in alternation, i.e.
30 sequentially, the time gap between administering the first compound and the second compound is preferably not too long in order to achieve a beneficial effect. Preferably, the time gap is less than half a day, most preferably less than 6 hours.

35 While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a

Boehringer Ingelheim Case 1-1522 Prio

20 -

pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising nevirapine and a compound of the formula (I) with one or more pharmaceutically acceptable carriers and, optionally, other
5 therapeutic and/or prophylactic ingredients.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub lingual), transdermal, vaginal or parenteral (including
10 intramuscular, sub-cutaneous and intravenous) administration in liquid or solid form or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well
15 known in the art of pharmacy. All methods include the step of bringing into association the active compound(s) with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

20

Pharmaceutical formulation suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active
25 ingredient(s); as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active ingredient(s) may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may
30 contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions,
35 syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives

Boehringer Ingelheim Case 1-1522 Prio

- 21 -

such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The pharmaceutical composition according to the invention
5 may also be formulated for parenteral administration (e.g.
~~by injection, for example bolus injection or continuous~~
infusion) and may be presented in unit dose form in
ampoules, pre-filled syringes, small volume infusion or in
multi-dose containers with an added preservative. The
10 compositions may take such forms as suspensions,
solutions, or emulsions in oily or aqueous vehicles, and
may contain formulatory agents such as suspending,
stabilizing and/or dispersing agents. Alternatively, the
active ingredient(s) may be in powder form, obtained by
15 aseptic isolation of sterile solid or by lyophilisation
from solution, for constitution with a suitable vehicle,
e.g. sterile, pyrogen-free water, before use.

Pharmaceutical formulations suitable for rectal
20 administration wherein the carrier is a solid are most
preferably presented as unit dose suppositories. Suitable
carriers include cocoa butter and other materials commonly
used in the art, and the suppositories may be conveniently
formed by admixture of the active compound(s) with the
25 softened or melted carrier(s) followed by chilling and
shaping in moulds.

When desired the above described formulations adapted to
give sustained release of the active ingredient(s) may be
30 employed.

The compositions, combinations, kit of parts, manufacture
and/or the use of the combinations according to this invention
are advantageous in the treatment and/or prophylaxis of viral
35 infections in a patient, preferably human retrovirus (HRV)
infections and hepatitis B, in particular HIV infections,
especially multiresistant HIV infections. Therefore this

Boehringer Ingelheim Case 1-1522 Prio

- 22 -

invention may offer an aid especially for highly treatment experienced patients suffering from multiresistant HIV. In addition to the treatment of said diseases, the combinations, formulations and compositions according to this invention can
5 be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The compositions, combinations, kit of parts, manufacture
10 and/or the use of the combinations according to this invention may also be beneficial in preventing perinatal transmission of human retroviral (HRV) infections, in particular HIV-1, from mother to baby. According to this method, nevirapine and a compound of the formula (I), preferably 3'-deoxy-3'-
15 fluorothymidine, and optionally further active compounds as described hereinbefore or hereinafter are administered in combination or alternation to the mother before giving birth.

The compositions, combinations, kit of parts, manufacture
20 and/or the use of the combinations according to this invention may also be beneficial in the treatment and/or prophylaxis of other HIV/AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological conditions, anti-HIV antibody positive
25 and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

Therefore, patients to be treated would be especially those individuals:

- 30 1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum; and/or
2) in the case of HIV, having either a asymptomatic HIV infection or a symptomatic AIDS defining infection such as i)
35 disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia,

Boehringer Ingelheim Case 1-1522 Prio

- 23 -

iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm³ in the peripheral blood.

- 5 The pharmaceutical combination according to this invention can be tested for additive and synergistic activity against HIV according to a number of assays known in scientific and public literature, including the one described in the WO 98/44913 and WO 00/51641, which are included herein by way of reference.

10

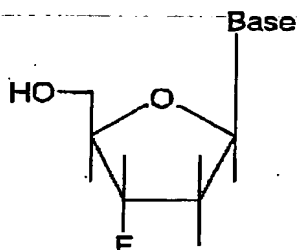
Boehringer Ingelheim Case 1-1522 Prio

- 24 -

Claims:

1. A pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)

5



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

10

2. The pharmaceutical composition according to claim 1 wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

15

3. The pharmaceutical composition according to claim 1 wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

20

4. The pharmaceutical composition according to one or more of the claims 1 to 3 wherein nevirapine and the at least one compound of formula (I) are present in a synergistic ratio.

25

5. The pharmaceutical composition according to one or more of the claims 1 to 4 wherein nevirapine and the at least one compound of the formula (I) are present in a

30

Boehringer Ingelheim Case 1-1522 Prio

- 25 -

ratio between about 1:250 to about 250:1.

6. The pharmaceutical composition according to claim 5 wherein nevirapine and the at least one compound of the formula (I) are present in a ratio between about 1:50 to about 50:1.

7. The pharmaceutical composition according to one or more of the claims 1 to 6 further comprising a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

10

8. The pharmaceutical composition according to claim 7 wherein (a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2'-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

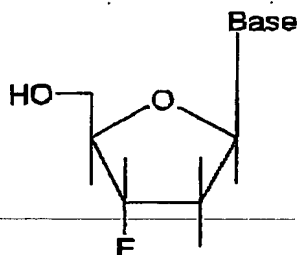
9. The pharmaceutical composition according to one or more of the claims 1 to 8 with at least one pharmaceutically acceptable carrier.

10. The pharmaceutical composition according to one or more of the claims 1 to 9 for use in the treatment or prophylaxis of human retroviral (HRV) infections.

11. Use of nevirapine in combination or alternation with at least one antiviral active compound of formula (I)

Boehringer Ingelheim Case 1-1522 Prio

- 26 -



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or
5 prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

12. The use according to claim 11, wherein the compound of
formula (I) is 3'-deoxy-3'-fluorothymidine, or a
10 pharmaceutically acceptable salt or prodrug thereof.

13. The use according to claim 11, wherein the compound of the
formula (I) is FLG or a pharmaceutically acceptable salt or
prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-
15 valyloxy)-propionyl]guanosine or a pharmaceutically acceptable
salt thereof.

14. The use according to claim 11, 12 or 13 in the prophylaxis
or treatment of a human retroviral infection (HRV) in a
20 patient.

15. The use according to one or more of the claims 11 or 14 in
the prophylaxis or treatment of a multiresistant HIV infection
in a patient.

25 16. The use according to one or more of the claims 11 to 15
for preventing perinatal transmission of a human retroviral
(HRV) infection from mother to baby.

Boehringer Ingelheim Case 1-1522 Prio

- 27 -

17. The use according to one or more of the claims 11 to 16, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a synergistic ratio.

5

18. The use according to one or more of the claims 11 to 17, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a ratio between about 1:250 to about 250:1.

10

19. The use according to claim 18, wherein nevirapine and the at least one compound of formula (I) are administered to the patient in combination or alternation in a ratio between about 1:50 to about 50:1.

15

20. The use according to one or more of the claims 11 to 19 in combination or alternation with a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

20

21. The use according to claim 20 wherein

(a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

25

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

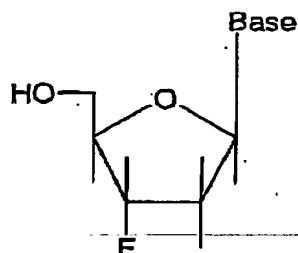
30

22. Use of nevirapine in combination with at least one antiviral active compound of formula (I)

35

Boehringer Ingelheim Case 1-1522 Prio

- 28 -



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or
5 prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

23. The use according to claim 22, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a
10 pharmaceutically acceptable salt or prodrug thereof.

24. The use according to claim 22, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable
15 salt thereof.

25. The use according to claim 22, 23 or 24, wherein nevirapine is used in combination with said compound of the
20 formula (I) and a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

26. The use according to claim 25 wherein
(a) the compound of the formula (I) is 3'-deoxy-3'-
25 fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt
30 thereof, or

Boehringer Ingelheim Case 1-1522 Prio

- 29 -

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

5

27. The use according to one or more of the claims 22 to 26 for the manufacture of a medicament for the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

10 28. The use according to one or more of the claims 22 to 27, wherein the medicament is a single dosage form.

29. The use according to one or more of the claim 22 to 27, wherein the medicament is a multiple dosage form.

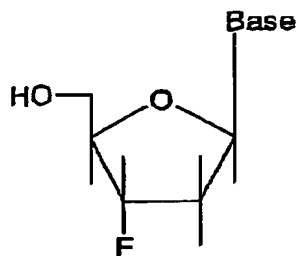
15

30. A kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising

(a) a first containment containing a pharmaceutical composition comprising nevirapine and at least one

20 pharmaceutically acceptable carrier, and

(b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)



I

25

wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable

30 carrier.

Biohringer Ingelheim Case 1-1522 Prio

- 30 -

31. The kit of parts according to claim 30, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

5

32. The kit of parts according to claim 30, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof.

10

33. The kit of parts according to claim 30, 31 or 32 for use in the prophylaxis or treatment of a human retroviral (HRV) infection in a patient.

15

34. The kit of parts according to one or more of the claim 30 to 33 further comprising a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

20

35. The kit of parts according to claim 34 wherein (a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable salt thereof, or

25

(b) the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, and the further NRTI is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof.

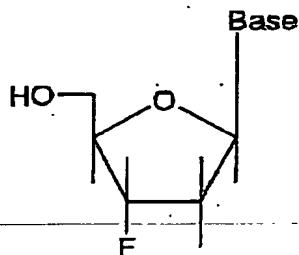
30

36. A manufacture comprising nevirapine and at least one antiviral active compound of formula (I)

35

Boehringer Ingelheim Case 1-1522 Prio

- 31 -



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or
5 prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

37. The manufacture according to claim 36, wherein the compound of formula (I) is 3'-deoxy-3'-fluorothymidine, or a
10 pharmaceutically acceptable salt or prodrug thereof.

38. The manufacture according to claim 36, wherein the compound of the formula (I) is FLG or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine or a pharmaceutically acceptable
15 salt thereof.

39. The manufacture according to claim 36, 37 or 38 for use in combination or alternation in the prophylaxis or treatment of a
20 human retroviral (HRV) infection in patient.

40. The manufacture according to one or more of the claims 36 to 39 further comprising a further NRTI, or a pharmaceutically acceptable salt or prodrug thereof.

25

41. The manufacture according to claim 40 wherein
(a) the compound of the formula (I) is 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof; and the further NRTI is FLG or a
30 pharmaceutically acceptable salt or prodrug thereof, in

Boehringer Ingelheim Case 1-1522 Prio

- 32 -

particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-
propionyl]guanosine or a pharmaceutically acceptable salt
thereof, or

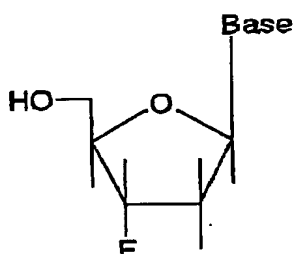
- (b) the compound of the formula (I) is FLG or a
5 pharmaceutically acceptable salt or prodrug thereof, and the
further NRTI is 3'-deoxy-3'-fluorothymidine, or a
pharmaceutically acceptable salt or prodrug thereof.

Boehringer Ingelheim Case 1-1522 Prio

- 33 -

Summary

In accordance with the present invention there is provided a pharmaceutical composition useful for the treatment or
5 prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)



I

wherein Base is selected from the group consisting of thymine,
10 cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

